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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,409	11/14/2000	Leisa Johnson	ONYX1033ord	5051

7590 03/17/2003

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 03/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/714,409	Applicant(s) Jonhson
	Examiner Dave Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 13, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above, claim(s) *6 and 13* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 7-12, and 14-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election without traverse of the species of Ad E1a promoter in the response filed August 19, 2003 is acknowledged. Claims 6 and 13 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species

Claims 1-5, 7-12, 14-16, to which the following grounds of rejection are applicable, are pending.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 8, 9, 15, 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a genus of tissue-specific replication-conditional vectors comprising a heterologous E2F responsive tissue-specific transcriptional regulatory sequence operably linked to the coding region of a viral gene that is essential for replication of said vector. The application only provides a sufficient description of a tissue-specific replication conditional adenovirus vector comprising a heterologous E2F responsive tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for replication of said vector. In order to practice the full scope of the claimed invention, one skilled in the art would turns for guidance from the as-filed specification for a description of the material(s) essential for the practice the full scope of the claimed invention, *e.g.,* genes essential for the replication of its respective virus vector, and its position in the vector genome for insertion of a heterologous tissue-specific transcriptional regulatory sequence. However, other than detailed description of preparation

and making of the claimed tissue-specific replication conditional adenovirus vector, the as-filed specification including its incorporated references do not provide a description of the essential material(s) as required by the full scope of the presently pending claims. Thus, it is not apparent to one skilled in the art that on the basis of the written description of this instant application, all other vector sequences, and/or coding sequences essential for replication of vectors other than the adenovirus vector are readily available for the practice the claimed invention. Claiming all nucleic acid vectors that achieve a result without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Claims 1-5, 7-10, 15, 16 are rejected under 35 U.S.C. 112, first paragraph, are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene; and

A method for killing cancer cells, comprising the steps of directly injecting to cancer cells a replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene.

The specification does not reasonably provide enablement for any and/or all other adenovirus vectors as claimed including claimed embodiments contemplating the use of tissue specific regulatory sequences that are not heterologous to adenovirus in the making of the claimed vectors, and/or the concept of adenovirus gene product(s) other than the E1a gene product, *e.g.* E4 gene product(s), to activate a second regulatory sequence located anywhere in the claimed adenovirus vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, since the claimed invention embraced by claims 1-2, 8, 9, 15, 16 is not supported by a sufficient written description (for possessing of the full scope of the claims for the reasons set forth above,

one skilled in the art would not known how to use and make the full scope of the claimed invention so that it would operate as intended without undue experimentation.

In addition, it is apparent from the as-filed specification and the prior art cited in pages 3-6 of the as-filed specification that in order to make and use the claimed invention when read within the context of the as-filed specification, an E2F responsive promoter must be operably linked to an adenovirus immediate early gene so as to render the replication of the modified adenovirus vector conditional, thereby exhibiting applicant's intended application of the vector for selectively killing neoplastic cells with little or no killing on non neoplastic cells (page 6 of the specification). It is not apparent how a skilled artisan makes and uses an adenovirus vector comprising an E2F responsive promoter operably linked to any other adenovirus gene so as to achieve applicant's intended application of an tissue specific and replication competent adenovirus vector. Moreover, it is well-established in the prior art of record, as evidenced by numerous cited prior art from the as-filed specification, that a sufficient amount of an adenovirus early gene intended targeted for its controllable transcriptional activity must be generated in order to replicate the modified adenovirus vectors inside transfected neoplastic cells. Within this context, the as-filed specification and the prior art of record only provides sufficient guidance for achieving this controllable transcriptional activity is teaching of employing an operable linkage of an E2F responsive promoter to an adenoviral immediate early gene in an adenovirus vector. As such, it is apparent on the basis of the as-filed specification and the prior art of record that only the subject matter drawn to a replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene is reasonably enabling at the time the invention was made.

Notwithstanding the above outstanding issues, claim 16 is readable on an *in vivo* method of propagating any replication competent viral vector in cancer cells without little or no killing of non-neoplastic cells in any cancer cells bearing animal so as to produce a therapeutically relevant effect. The state of the art exemplified by Russell (European Journal of Cancer, Vol. 30A, 8:1165-1171, August 1994) states that "cell-specific utilisation of the albumin (liver specific) and immunoglobulin (B-cell specific) promoters has been demonstrated within non-replicating adenovirus genomes but cell specificity was partially lost after

replication of the viral DNA", and that the stoichiometry and kinetic of gene regulation by cellular transcription factors must be known for engineering the promoters of replicating vectors for tissue-specific, transformation-dependent expression (p. 1168, column 2). In addition, Miller *et al.* (Human Gene Therapy, Vol. 8, pp. 803-815, 1997) teaches (page 807, column 1) that problems with vectors for tissue specific replication include:

- "Interference of vector sequences with regulatory sequences, particularly where the vector is derived from a virus";
- "Interference from sequences after vector integration, *i.e.,* positional effects";
- "Non specific effects on host transcription".

More specifically, Miller *et al.* states:

"It was found that PKA activators such as aminophylline enhanced expression of cytokine genes driven by the tyrosinase promoter in melanoma but not fibroblast cell lines (Miller *et al.,* 1995). Unfortunately, this effect could not be duplicated *in vivo* (possibly the activity of the tyrosinase promoter differs between a there-dimensional tumor mass *in vivo* and a two-dimensional monolayer *in vitro*".

In addition, Vile *et al.* (Molecular Medicine Today, Vol. 4, 2:84-92, 1998, p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems", and that "the combinations of these elements in certain configurations of these elements might be successful in the context of one vector (such as plasmid DNA), but their specificity might be altered or lost in a different context (such as retrovirus or adenovirus)". As to the problem of adenoviral leakiness, Gomez-Navarro *et al.* (European J. of Cancer, Vol. 35, 6:867-885, 1999) states that "it has been reported that certain tumour-specific regulatory elements lose their specificity in the context of an adenoviral vector" (p. 878, column 2, last par.), and that "major problems remain to be solved before these approaches can become effective and common place strategies for cancer (p. 881, column 1, last par.), Moreover, Yanez (Gene Therapy, 5:149-159, 1998) states:

While Gene targeting has been achieved both in human cell lines and in nontransformed, primary human cells, its low efficiency has been a major limitation to its therapeutic potential. Gene therapy by in vivo gene targeting is therefore impractical without dramatic improvements in targeting efficiency.

Thus, it is not apparent how any of the disclosed tissue-specific vectors when used in the context of an application of an E2F responsive promoter, let alone other unspecified E2F responsive regulatory sites, is distributed and/or targeted only in a desired *in vivo* cancer cells for replication and subsequent expression of a heterologous gene, thereby generating any therapeutically useful effect, particularly on the basis of applicant's disclosure and given the doubts expressed by the art of record.

With regard to claims directed to tissue-specific replication-conditional adenoviral vectors (which is a preferred species of the claimed invention), the adenoviral genes, E1b, E2, E1A, and E4 (all essential for replication of adenovirus vectors) encode proteins whose functions are dissimilar with each other. Each of these genes or regions requires a certain level of expression to support adenoviral replication. Note also cited prior art of Hallenbeck (WO 96/17053) teaches that the expression levels of adenoviral genes essential for replication, *e.g.,* E1 and E4, must be carefully regulated in order to averse toxicity effect of the adenoviral genes upon the cells or tissues transformed with adenovirus vectors. Since it is known in the art (Russell, Vile *et al.*) that tissue-specific cellular promoters activate constitutive expression of a transgene in a target tissue thereby leading to an uncontrollable replication of the introduced replication competent adenovirus vectors, it is not apparent how the expression levels of E4 gene, for example, are regulated *in vivo* from the claimed adenoviral vectors in order to avoid the toxicity to normal cells *in vivo* (due to leakage of the adenovirus replicons to nearby tissues and cells) before a therapeutically useful effect can be generated. There is no discussion in the specification of expression levels necessary to achieve appropriate expression for specific replication in a target tissue or cells *in vivo* so that toxicity would not occur to an *in vivo* subject before a therapeutically useful effect can be generated.

More specifically as to claimed methods of distributing a polynucleotide in a tissue *in vivo* using any of the claimed vectors, the claims encompass gene-targeted therapy in any subject including a human and

implanted cells containing the claimed vector for generating a therapeutic effect. The application contemplates that claimed cancer gene therapy method using any known routes of administration would deliver and express the claimed viral vectors in any target cancer site *in vivo* in a sufficient amount required for its conditional replications so as to generate a therapeutically killing effect only in those cancer cells, with little or no killing of non-neoplastic cells. However, the state of the art exemplified by Anderson (Nature, Vol. 392, pp. 25-30, April 1998) indicates that major considerations for any gene transfer or gene therapy protocol involve issues including amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the claimed methods. In addition, Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph).

More specifically as to the state of the art of cancer gene therapy, Mastrangelo *et al.* (Seminars in Oncology, Vol. 23, No. 1:4-21, 1996) teaches:

- "c[C]ritical to the success of gene therapy is the efficient gene transfer (transfixing) of a functional gene to the target cell. This has proven a major stumbling block, particularly for in vivo gene transfer" (page 10, column 1, first paragraph); and
- "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (page 13, column 2, first paragraph).

Meng *et al.* (Gene Therapy of Cancer, Chapter I, pp. 3-20, 1999) teach that factors including specific genes used for a treatment, gene delivery vectors, routes of administration, and gene expression are all critical for the success of a gene therapy method (pages 4-6). For example, Meng *et al.* teach that "it is difficult to prepare sufficiently high titers of retroviruses for *in vivo* gene therapy", that "the most significant drawback to adenoviruses, however, is that they elicit a strong host immune response", and that "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene" (p. 4, column 2, last paragraph). Meng *et al.* further teach that "although animal studies have suggested low toxicity and excellent efficacy, these investigations have been limited by the use of immuno-deficient mice" (p. 6, column 1).

In fact, Meng *et al.* teach that other than intratumor injection, delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers to the delivery of the target genes (p. 6, column 1). For example, Meng *et al.* state:

> "In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass." (page 6, column 1).

While transient gene expression has been observed in cells *in vivo* at the time of filing using routes of administration other than intratumoral administration, it is not apparent how a randomly transient gene expression in a tumor bearing animal is reasonably correlated to any meaningful or sufficient amounts of the claimed viral vectors inside only target cancer cells so as to produce only targeted killing effects in the cancer cells, particularly given the doubts expressed in the art of record. The skilled artisan then next turns for evidence from applicant 's disclosure in order to practice the claimed methods. However, the as-filed specification does not provide sufficient guidance and/or evidence to overcome and/or resolve the

outstanding issues and barriers expressed by the art of record with respect to cancer targeted gene therapy of using any viral vector. As such, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any other mode of delivery other than intratumoral administration.

In view of the reasons set forth above, the nature of the invention, the unpredictability of gene therapy, and the breadth of the claims, it is not apparent as to how one skilled in the art practices the full scope of the claimed invention without undue experimentation.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-12, 14-16, readable on a replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene; and

A method for killing cancer cells, comprising the steps of directly injecting to cancer cells a replication competent adenovirus vector comprising the human E2F1 responsive promoter operably linked to an adenovirus immediate early gene,

are rejected under 35 USC 102(e) as being anticipated by Yu (US 2001/005333352).

Yu teaches the same throughout the reference, specifically pages 7, 9 and 13 and the claims.

More specifically, pages 7, 11, and 13, respectively, state:

> **[0088]** Accordingly, in one embodiment, the invention provides an adenoviral vector in which an adenoviral gene (preferably a gene necessary for replication) is under transcriptional control of a cell status-specific TRE, wherein the cell status-specific TRE comprises a cell cycle-activated, or cell-cycle specific, TRE. In one embodiment, the cell cycle-activated TRE is an E2F1 TRE. In one embodiment, this TRE comprises the sequence depicted in **FIG. 3** and SEQ ID NO:2.

> **[0105]** When a cell status-specific TRE is used with an adenovirus gene that is essential for propagation replication competence is preferentially achievable in the target cell expressing cell status. Preferably, the gene is an early gene, such as E1A, E1B, E2, or E4. (E3 is not essential for viral replication.) More preferably, the early gene under cell status-TRE control is E1A and/or E1B. More than one early gene can be placed under control of an cell status-specific TRE. Example 1 provides a more detailed description of such constructs.

> **[0139]** The adenoviral vectors may be delivered to the target cell in a variety of ways, including, but not limited to, liposomes, general transfection methods that are well known in the art (such as calcium phosphate precipitation or electroporation), direct injection, and intravenous infusion. The means of delivery will depend in large part on the particular adenoviral vector (including its form) as well as the type and location of the target cells (i.e., whether the cells are in vitro or in vivo).

Thus, the reference does teach the same and in the absence of evidence to the contrary, anticipates the claimed embodiments.

Claims 1-5, 7-12, 14-16, readable on a replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene; and

A method for killing cancer cells, comprising the steps of directly injecting to cancer cells a replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene,

are ejected under 35 U.S.C. 103(a) as being unpatenble over either Hallenbeck (US Pat No. 5,998,205) or Gregory (US 2003/0026789), taken with Fine (WO 98/13508).

Both Hallenbeck (columns 4, 6, 10-14, particularly columns 13, and 27-28) and Gregory (pages 4, 5 and 7) teaches a replication-competent adenovirus vectors comprising a tumor specific transcription regulatory sequence operably linked to at least one replication gene of the adenoviral vector, and the use of the vectors to kill cancer cells by contacting the cancer cells with the adenovirus vectors. Both references teach that tissue specific or cell specific regulatory sequences such as promoters and enhancers are operably linked to virus genes essential for replication functions, and that these genetic sequences are

specifically activated or derepressed in the target tissue, and the invention are essential directed to cancer gene therapy methods for tissue-specific replication using these vectors in target cancer cells.

Hallenbeck and Gregory do not teach that the tissue or cell specific promoter is an E2F responsive promoter. However, at the time the invention was made, Fine teaches and discloses the advantages of using an E2F responsive promoter (page 9) as a tumor specific promoter so as to improve the killing of tumor cells using any cancer gene therapy vector available in the prior art of record (pages 3 and 4). More specifically, Fine teaches that a vector such as an adenoviral vector (page 12 bridging page 13) can be used to carry an E2F responsive promoter operably linked to a heterologous gene of interest, preferably encoding a negative potentiator (page 4), and that the use of such vectors result in high selectivity *in vivo* between malignant and non-malignant cells (page 4).

It would have been obvious for one of ordinary skill in the art to employ an E2F responsive promoter (page 9 of Fine) as the cancer cell specific promoter in the adenoviral vector system of either Hallenbeck or Gregory. One of ordinary skill in the art would have been motivate to employ the E2F responsive promoter as the cancer cell specific promoter in the adenoviral vector system of either Hallenbeck or Gregory because Fine teaches and discloses the advantages of using an E2F responsive promoter as a tumor specific promoter so as to improve the killing of tumor cells using any cancer gene therapy vector available in the prior art of record, and because both Hallenbeck and Gregory teaches that if a target tissue is cancer cells containing target tissue, any promoter specific to the tissue or cancer cells of the tissue can be used in an adenoviral vector so as to control the expression of an adenovirus early gene in the tissue, wherein expression of the early gene as the result of the induced activity of the promoter would result in the killing of the cancer cells in the target tissue.

Thus, the claimed invention as a whole was *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER